UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte NORBERT MAURER, KIM F. WONG and PIETER R. CULLIS

Appeal No. 2005-0937
Application No. 10/019,199

ON BRIEF

Before ELLIS, SCHEINER and MILLS, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 13-32, all the claims pending in the application. Claims 1-12 have been cancelled.

Claims 13 and 14 are representative of the subject matter on appeal and read as follows:

> 13. A method for preparing fully lipid-encapsulated therapeutic agent particles of a charged therapeutic agent comprising the steps of
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> combining a lipid composition comprising preformed lipid vesicles, a charged therapeutic agent, and a destabilizing agent to form a mixture of preformed vesicles and therapeutic agent in a destabilizing solvent, wherein said

destabilizing solvent is effective to destabilize the membrane of the preformed lipid vesicles without disrupting the vesicles,

incubating the mixture for a period of time sufficient to allow the encapsulation of the therapeutic agent within the preformed lipid vesicles, and

removing the destabilizing agent,

wherein the preformed lipid vesicles comprise a charged lipid which has a charge which is opposite to the charge of the charged therapeutic agent and a modified lipid having a steric barrier moiety for control of aggregation, and wherein the modified lipid is present in the preformed vesicles in an amount effective to retard, but not prevent, aggregation of the preformed vesicles.

14. The method of claim 13, wherein the charged lipid in the preformed lipid vesicles comprises a cationic lipid and the therapeutic agent is an anionic therapeutic agent.

The references relied upon by the examiner are:

Zalipsky et al. (Zalipsky)	6,365,179	Apr. 2, 2002
Hope	6,447,800	Sep. 10, 2002
Wheeler et al. (Wheeler)	5,976,567	Nov. 2, 1999
Semple et al. (Semple)	WO 98/51278	Nov. 19, 1998

Schubert et al. (Schubert), "Loading of preformed liposomes with high trapping efficiency by detergent-induced formation of transient membrane holes." Chemistry and Physics of Lipids, vol. 58, pp. 121-129 (1991).

Malone et al. (Malone), "Cationic liposome-mediated RNA transfection." Proc. Natl. Acad. Sci. USA, vol. 86, pp. 6077-6081 (1989).

The claims stand rejected as follows:

I. Claims 13-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hope in view of Wheeler or Semple.

II. Claims 13-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hope in view of Malone and Zalipsky.

III. Claims 13-20 and 25-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Schubert in view of Malone and either Zalipsky or Semple.

We have carefully considered the respective positions of both the appellants and the examiner and find ourselves in substantial agreement with that of the appellants. Accordingly, we reverse Rejections I-III.

Background and Discussion

As indicated by the claims above, the present invention is directed to a method of making particles of lipid-encapsulated therapeutic agents. The invention is said to be particularly advantageous for encapsulating nucleic acid particles for use in antisense therapy or gene therapy. Specification, p. 1, lines 3-4. According to the specification, prior to the appellants' invention it had not been possible to manufacture, in large scale, lipid-encapsulated therapeutic agents wherein there is a significant electrostatic interaction between the lipid and said agents. Id., lines 21-23. The problem is said to be due to the aggregation which occurs when a charged lipid is mixed with an oppositely-charged therapeutic agent. Id., lines 23-25. The aggregation is said to result in "a milky flocculent mass which is not useable for further processing, let alone for therapeutic use." Id., lines 25-27. The present method of encapsulating a charged therapeutic agent is said to overcome the problem of aggregation.

I.

The examiner argues that Hope discloses a method of preparing liposomes which involves combining formed liposomes with an active agent and an organic solvent (viz., 10% ethanol), and diluting said solvent after a period of time. Answer, p. 3. The examiner further argues that the only difference between the claimed method of making lipid encapsulated therapeutic agent particles and the method taught by Hope is that the patent does not disclose the use of cationic lipids and the removal of the organic solvent. Id., p. 4. To that end, the examiner relies on Wheeler which is said to disclose a method of making liposomal formulations which comprise cationic lipids (such as DOTAP and DOTMA), PEG-derivatized phospholipids and nucleic acids, wherein said method employs the use of ethanol. Id. According to the examiner, Wheeler discloses the removal of ethanol using art-recognized methods. Id. The examiner acknowledges that Wheeler does not describe the use of pre-formed liposomes.

Alternatively, the examiner argues that Semple discloses (i) compositions containing DOPAP, DSPC, and cholesterol; and (ii) that "PEG-derivatized lipids provide steric stablization and prevent the aggregation of particles." Answer, p. 4.

The examiner concludes that

> The use of cationic lipids in the method of Hope, if the active agent involves a nucleic acid would have been obvious to one of ordinary skill in the art since Wheeler teaches that cationic lipids are efficient in transfecting cells with nucleic acids in a similar method of preparation involving ethanol. The removal of the already diluted ethanol in the external medium of Hope if it is deemed undesirable would have been obvious to one of ordinary skill in the art since Wheeler shows that external ethanol can be removed by art known methods.

> The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH [emphases added] [Answer, para. bridging pp. 4-5].

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Cutting to the chase, we find that the examiner has not even begun to address all the limitations present in the only independent claim on appeal; i.e., claim 13. Rather than beginning with the independent claim, the examiner has jumped from claim to claim pointing to a teaching of a cationic lipid (claim 14, et seq), a nucleic acid (claim 16), ethanol as a destabilizing agent (claim 21), and the presence of citric buffer (claim 24) and cobbled together a rejection which lacks sufficient reason to combine the various disclosures of these limitations. We point out with respect to claim 24, for example, the examiner has not pointed to any teachings in the applied prior art which would have suggested including the citric buffer in the method of encapsulating an active agent described by Hope and appears to have conceded that its presence would not have been obvious to one of ordinary skill in the art. What is missing at the outset

in the examiner's rejection is a suggestion in the applied prior art to modify the method of loading pre-formed liposomes taught by Hope to arrive at a method of making a lipid-encapsulated therapeutic agent which involves both (i) a pre-formed lipid vesicle wherein the lipid composition comprises a charged lipid as well as a modified lipid; and (ii) a therapeutic agent which has a charge which is opposite that of the charged lipid. We find that the examiner's arguments with respect to "if" the active agent was a nucleic acid, and "if" the presence of a substrate removed in the claimed method was "deemed undesirable," are not based on any teachings in the applied prior art, but have been devised "using the applicant's structure as a template and selecting elements from references to fill the gaps." In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Thus, we find that the examiner has engaged in impermissible hindsight to arrive at the conclusion that the claimed invention would have been obvious over Hope and Wheeler or Semple. In re Fritch, 972 F.2d at 1266, 23 USPQ2d at 1784; Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983)("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

Accordingly, we reverse Rejection I.[1]

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[1] Although we agree with many of the arguments made by the appellants on pages 5-9 of the Brief, given our disposition of Rejection I, we need not reach them to

II.

In addition to the teachings of Hope as stated above, the examiner argues that Malone discloses that "the use of cationic liposomes containing DOTMA is an efficient way of RNA transfection." Answer, p. 10. In addition, the examiner argues that Zalipsky disloses that liposome formulations which comprise modified polymer-derivatized lipids such as PEG-phospholipids extend the circulation time of said formulations in the blood stream. Id. The examiner further argues that Zalipsky discloses the use of ethanol in the preparation of the liposomes as well as the removal of said ethanol by diafiltration. Id.

The examiner concludes that

> The use of cationic lipid, DOTMA in the method of Hope, if the active agent involves a nucleic acid would have been obvious to one of ordinary skill in the art since Malone teaches that this cationic lipid is efficient in transfecting cells with nucleic acids. The removal of the already diluted ethanol in the external medium of Hope if it is deemed undesirable would have been obvious to one of ordinary skill in the art since Zalipski teaches that the external ethanol can be removed by diafiltration. The use of modified lipids in Hope would have been obvious to one of ordinary skill in the art since Zalipski also teaches that these lipids extend the circulation time of the liposomes. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH [emphases added] [Answer, p. 10].

Here, we agree with the appellants that this rejection is substantially the same as Rejection I with Malone providing the teachings of charged (cationic) lipids and Zalipsky disclosing a method of making liposomes using, inter alia, modified lipids such as PEG-phospholipids, and ethanol. The substitution of the secondary references does nothing

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reverse.

to overcome the deficiencies we pointed out with respect to Rejection 1. That is, the examiner's rejection lacks a suggestion in the applied prior art to modify the method of loading pre-formed liposomes taught by Hope to arrive at a method of making a lipid-encapsulated therapeutic agent which involves both (i) a pre-formed lipid vesicle wherein the lipid composition comprises a charged lipid as well as a modified lipid; and (ii) a therapeutic agent which has a charge which is opposite that of the charged lipid. Thus, we find that the examiner has engaged in hindsight to arrive at the conclusion that the claimed invention would have been obvious over Hope, Malone and Zalipsky. In re Fritch, 972 F.2d at 1266, 23 USPQ2d at 1784; Interconnect Planning Corp. v. Feil, 774 F.2d at 1138, 227 USPQ at 547; W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d at 1553, 220 USPQ at 312-313.

Accordingly, Rejection II is reversed.

III.

Rather than relying on Hope as the primary reference, the examiner turns to the teachings of Schubert with respect to a method of "loading preformed liposomes by detergent-induced (destabilizing agent-induced) formation of transient membrane holes." Answer, p. 11. The examiner argues that Schubert's method "involves the incubation of the preformed liposomes with the active agent such as nucleic acids and removal of the detergent." Id. The examiner acknowledges that Schubert does not disclose the use of a cationic lipid or a modified lipid. Id. To that end, the examiner

relies on the teachings of Malone and Zalipsky or Semple as described above in Rejections I and II.

The examiner contends that

> The use of cationic lipid, DOTMA in the method of Schubert would have been obvious to one of ordinary skill in the art since Malone teaches that this cationic lipid is efficient in transfecting cells with nucleic acids. The use of modified lipids in Schubert would have been obvious to one of ordinary skill in the art since Zalipski also teaches that these lipids extend the circulation time of the liposomes or since WO 98 [Semple] teaches their ability to sterically stablize the particles. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH; one of ordinary skill in the art would be motivated to use citrate buffer since WO [Semple] teaches that it is commonly used in liposomal preparations containing nucleic acids [Answer, para. bridging pp. 11-12].

Here, we find that the examiner has substituted the primary reference, Hope, with Schubert. Again, we find that the only suggestion to make a lipid-encapsulated therapeutic agent which (i) comprises a pre-formed vesicle having a charged lipid, a modified lipid and a therapeutic agent wherein the therapeutic agent has a charge which is opposite that of the charged lipid; and (ii) involves the use of a destabilizing agent which does not disrupt the pre-formed vesicle, as well as the removal of said agent, comes from the appellants' disclosure. Schubert does not disclose the encapsulation of nucleic acids, or any other therapeutic agent having the opposite charge of the lipid liposome membrane described therein. As discussed above, the only motivation to combine the teachings of the applied prior art comes from the appellants' specification. Thus, we find that the examiner has relied on hindsight in reaching his conclusion of obviousness. In re Fritch, 972 F.2d at 1266, 23 USPQ2d at

1784; Interconnect Planning Corp. v. Feil, 774 F.2d at 1138, 227 USPQ at 547; W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d at 1553, 220 USPQ at 312-313.

Accordingly, Rejection III is reversed.

REVERSED

Joan Ellis
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

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